Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

E-glass microfibres of representative composition

EC number: -
CAS number: -

CLH-O-0000001412-86-34/F

Adopted

4 December 2014

4 December 2014

CLH-O-0000001412-86-34/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemicals name: E-glass microfibres of representative composition

EC number: -

CAS number: -

The proposal was submitted by **France** and received by RAC on **14 February 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

France has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **5 March 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 April 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 December 2014.**

The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

RAC adopted the opinion that **E-glass microfibers of representative composition** should be classified and labelled as follows:
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	014-046-00-4	e-glass microfibres of representative composition; [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO2 50.0-56.0%, Al2O3 13.0-16.0%, B2O3 5.8-10.0%, Na2O <0.6%, K2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe2O3 <0.5%, F2 <1.0%. Process: typically produced by flame attenuation and rotary process. (Additional individual elements may be present at low levels; the process list does not preclude innovation).]	-	-	Carc. 1B	H350i	GHS08 Dgr	H350i			R
RAC opinion	014-046-00-4				Carc. 1B	H350i	GHS08 Dgr	H350i			A
Resulting Annex VI entry if agreed by COM	014-046-00-4				Carc. 1B	H350i	GHS08 Dgr	H350i			A

RAC general comment

In annex VI of Regulation 1272/2008 (CLP), fibres with a harmonised classification are man-made vitreous fibres (MMVF) which are subdivided into two different entries (see table below).

Index No	International Chemical Identification	Hazard Class and Category Code(s)	Hazard statement Code(s)	Notes
650-016-00-2	Mineral wool, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na_2O + K_2O + CaO + MgO + BaO) content greater than 18 % by weight]	Carc. 2	H351	A, Q, R
650-017-00-8	Refractory Ceramic Fibres, Special Purpose Fibres, with the exception of those specified elsewhere in this Annex; [Man-made vitreous (silicate) fibres with random orientation with alkaline oxide and alkali earth oxide (Na_2O + K_2O + CaO + MgO + BaO) content less or equal to 18 % by weight]	Carc. 1B	H350i	A, R

The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 cover '*mineral wool*' and '*Refractory Ceramic Fibres, Special Purpose Fibres*', respectively. These entries are differentiated by name and the chemical composition with respect to the content of alkaline oxides and alkali earth metal oxides with 18 % by weight being the cut-off point. Their hazardous properties and harmonised classifications (CLH) are 'suspected human carcinogens' (Carc. 2) and 'presumed human carcinogens' (Carc. 1B), respectively.

The CLH proposal originally submitted by the Dossier Submitter (DS) refers to glass fibres within the glass wool category and therefore continuous filaments are not within scope of the proposal. In addition, a new entry in Annex VI needs to be created for the E-glass microfibres of representative composition. This class of glass wool fibres consists of fine glass fibres forming a mass resembling wool; individual fibres are defined as being over 5 µm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fibre is at least three times as long as its width). There is considerable variation in the physico-chemical properties of individual fibres within this class, depending on the manufacturing process and end use. It is well-known that relatively small changes in composition can result in significant changes in the optical and electrical properties of the glass fibres. For example C-glass fibres are resistant to chemical attack, S-glass fibres have a high strength whereas E-glass fibres are poor conductors of electricity. A specific glass wool product often contains fibres with a wide range of diameters, as a result of the manufacturing process.

The manufacturing process also determines the particle length and diameter of the fibres. The methods of manufacture determine whether a fibre is a "General Purpose Fibre" or a "Special Purpose Fibre". "Special Purpose Fibres" are characterised by having a diameter < 5µm while "General Purpose Fibres" are having a diameter > 5µm. A fibre of a given chemical composition can be either a "Special Purpose Fibre" or a "General Purpose Fibre" depending on the method of manufacture (E-glass fibres for example can be either general purpose insulation fibres or special purpose fibres). Special purpose fibres are referred to in this report as "microfibres" as this terminology is used in industry and is more representative than "special purpose". The typical process to produce the E-glass microfibres of representative composition is by flame attenuation and rotary process.

For cancer hazard identification, it is important that fibres are classified according to their biological activity, including their biopersistence *in vivo* (Bernstein, 2007). The E-glass microfibres considered in this document are characterised with respect to the contents of alkaline oxides and alkali earth metal oxides ($Na_2O+K_2O+CaO+MgO+BaO$) being greater than the current 18% by weight cut-off as described in existing Annex VI entries for fibres. E-glass microfibres have a lower alkaline oxides and alkali earth metal oxides content than glass fibres of representative composition and also a higher content of Al_2O_3 (Campopiano *et al*., 2014).

Recognising the range of biological effects induced by various types of glass fibres, France submitted a proposal for harmonised classification of E-glass microfibers. During the first public consultation (PC) of the CLH report (5 March to 19 April 2013), a number of issues were raised by manufacturers and downstream users including the incorrect composition and manufacturing process details, the confusion in the name between continuous filament glass fibres ("not respirable") and microfibres ("respirable "). In addition, manufacturers and downstream users proposed an alternative name for the substance. In November 2013, the French proposal was withdrawn for further consideration and in February 2014, a new dossier was submitted to ECHA by France on "E-glass fibres of representative composition" followed by a new PC from 5 March 2014 until 22 April 2014. After PC, the DS agreed to rename the "fibres" as "microfibres" to distinguish between respirable "E-glass microfibres" and "E-glass Continuous Filament Glass Fibres" which are not respirable.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

E-glass microfibres of representative composition [Calcium-aluminium-silicate fibres with random orientation with the following representative composition (% given by weight): SiO_2 50.0- 56.0%, Al_2O_3 13.0-16.0%, B_2O_3 5.8-10.0%, Na_2O <0.6%, K_2O <0.4%, CaO 15.0-24.0%, MgO <5.5%, Fe_2O_3 <0.5%, F_2 <1.0%] are proposed to be classified as Carc. 1B – H350i. The DS further proposed adding Note R, which, according to Annex VI of the CLP Regulation, states that the classification as a carcinogen needs not apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 µm.

The DS presented the available toxicology studies by different routes of exposure (inhalation, intraperitoneal, intratracheal, intrapleural) as well as a summary of the available human information. The DS concluded that the potential for carcinogenic effects is confirmed by inhalation in a well-designed study with E-glass microfibres. E-glass microfibres induce a marked macrophage reaction, alveolar fibrosis and hyperplasia which may indicate a progressive pathway to neoplastic transformation of respiratory cells, whereas glass microfibres of representative composition (analogous to commercial grade or type '475' glass microfibres and special purpose glass fibres with comparable chemical compositions of 'Evanite B' and 'Laucher B-glass') do not exhibit such effects by inhalation (Cullen, 2000). Besides, a comparison between the carcinogenic potential by the intraperitoneal route (Pott, 1984) shows that 32% of rats had abdominal tumours with E-glass microfibres, although only 4% of rats had abdominal tumours with type '475'-glass fibres.

Overall, the DS has concluded that E-glass microfibres of representative composition are presumed to be human carcinogens and should be classified as Carc. 1B – H350i under the CLP Regulation with note R assigned to the entry in Annex VI to the CLP Regulation.

Comments received during public consultation

No comments were submitted objecting to the proposed classification. Two MSCAs supported the classification, but suggested some editorial improvements and one MSCA requested additional substantiation of the proposed classification in order to fulfil the CLP requirement to demonstrate carcinogenicity of the E-glass microfibres in more than one species. Five industrial organisations indicated a need to rename the substances from "fibres" to "microfibres" which was supported by

the DS and also taken into account in this opinion. The CLH report will however not be updated but additional information will be available in Annex 2 to the opinion (Response to comments document, RCOM).

Assessment and comparison with the classification criteria

Summary of animal studies

Inhalation studies:

In the study of Cullen *et al*. (2000) the carcinogenic potency of E-glass fibres 104E, glass microfibres analogous to type '475' and amosite asbestos were compared after chronic inhalation exposure and after intraperitoneal injection in rats. Rats were exposed for 12 months to aerosol concentrations of 1000 fibres (longer than 5 µm)/mL, as measured by optical microscopy, for 7 h/day, 5 days/week. Subgroups of rats were examined for mean lung burden, early and late signs of fibrosis, and tumour incidence.

From the inhalation study using a subgroup of 43 animals exposed to E-glass (104E) microfibres, 10 (23%) rats had lung tumours (7 carcinomas, 3 adenomas) and 2 (5%) had mesotheliomas, whereas in 42 rats exposed to amosite asbestos, there were 16 (38%) lung tumours (7 carcinomas, 9 adenomas) and 2 (5%) mesotheliomas.

The E-glass fibres (104E) and amosite-treated animals had similar levels of fibrosis. In contrast, 38 (88%) rats treated with glass microfibres (100/475) had little fibrosis, 4 (10%) had lung tumours (adenomas), and no animal had mesotheliomas.

The study provided evidence for carcinogenicity of E-glass microfibres by the inhalation route of exposure.

The greater pathology induced by the E-glass microfibres, referred to as commercial type grade or type 104E, compared to the other glass microfibres (commercial grade or type 100/475 microfibres), might be partly explained by the greater numbers of long fibres retained in the lung after 12 months of inhalation. However, it is possible that modification of surface properties by extensive selective leaching of some glass components reduces the toxic potential of the commercial grade or type 100/475 microfibres.

At the end of 12 months of exposure, the mean number of grade or type 104E fibres of all lengths in the lungs was approximately double that for amosite, but two-thirds of that for 100/475 microfibres. For fibres longer than 15 µm, the mean grade or type 104E burden was similar to that for the amosite and more than twice that of the 100/475. After a 12-month recovery period, the retained lung burdens (of fibres of all lengths) were approximately 30% of those at 12 month for both microfibres, and somewhat higher (approximately 44%) for amosite. Amosite and 100/475 fibres longer than 15 µm were more persistent in the lungs than grade or type 104E fibres.

The chemical composition of grade or type 104E fibres did not appear to have been significantly altered by up to 24 months of residence in lung tissue, whereas the composition of type 100/475 was substantially altered over the same time period.

In a parallel intraperitoneal injection study, grade or type 104E caused considerably more mesotheliomas (21 rats out of 24) than 100/475 (8 rats out of 24). In addition, grade or type 104E appeared to be more active than amosite asbestos, since mesotheliomas appeared much more quickly in the grade or type 104E-treated animals. The results of this study demonstrated that two microfibre types, 100/475 and 104E, of similar dissolution rates, had markedly different potency in rats. In the opinion of the authors (Cullen *et al*., 2000), this contrast is only partly due to differences in numbers of long fibres and the differences in surface properties of the fibres, possibly due to proportionately greater leaching of 100/475 fibres, play an important role.

Intratracheal studies:
Two intratracheal instillation studies in hamsters were reported by the DS in the CLH report, but the exact type and composition of glass microfibres used (types '475', 'E' or '753') was not indicated by the authors (Feron *et al*., 1985; Mohr *et al*., 1984). They are inconclusive for the hazard assessment of E-glass microfibres. They are briefly described in the Background Document for information.

Intraperitoneal injection studies:

By intraperitoneal exposure, Cullen *et al*. (2000) showed an increase in the incidence of mesotheliomas. Besides, all studies from Pott (1984, 1987 and 1988) clearly report an increased incidence of abdominal tumours following exposure to E-glass microfibres by the intraperitoneal route. A dose-response related effect was observed in the studies of Pott (1976, 1984). It should, however, be noted that the type and composition of glass fibres is not indicated in the Pott (1976) study.

Intrapleural injection studies

There is no adequate study by this route for E-glass microfibres. According to the CLH report, there is a study on 'JM 104' type fibres (Monchaux *et al*., 1981 reported by IARC, 2002) conducted by the intrapleural route with uncertain significance for the assessment of the carcinogenicity of E-glass microfibres.

Summary of human studies

A case-control study did not show any association between laryngeal or hypopharyngeal cancers and microfibre exposure (Marchand *et al*., 2000) but the study included a very small number of microfibre-exposed subjects. In an historical cohort study (Marsh *et al*., 2001), an excess of respiratory cancer was observed in the general glass-fibre group of workers but not in the special–purpose glass fibres sub-group. The size of this sub-group was also limited. Overall, these data are not considered sufficient to draw any conclusion on the potential carcinogenic effects in humans.

Comparison with the classification criteria

According to criteria in Annex 1 of the CLP Regulation (Table 3.6.1), in order to classify a substance in Category 1B for carcinogenicity (i.e. presumed to have carcinogenic potential for humans), classification should be largely based on evidence derived from animal experiments which is sufficient to demonstrate animal carcinogenicity (presumed human carcinogen). It is further clarified in the CLP Regulation, Annex 1, Section 3.6.2.2.3.(b) "Carcinogenicity in experimental animals" that it is possible to conclude:

"*sufficient evidence of carcinogenicity if :*

a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in

(a) two or more species of animals or

(b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols".

An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence.

A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence,

site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites."

Glass microfibres are poorly soluble minerals which only undergo selective leaching and dissolution. Major determinants of toxicity are the form and size of the fibres, surface chemistry, and bio-persistence. Crystal structure, chemical composition, origin, and associated minerals, as well as trace contaminants, all modulate surface chemistry; and transformation, translocation, and solubility of the fibres in body fluids influence their biopersistence, a factor which modulates cumulative exposure (IARC, 2012). In relation to fibre dimension and deposition, one can assume that there exists a continuum of the carcinogenic potency of respirable fibres, which increases with length. Biopersistence of a fibre increases tissue burden, and therefore, may increase any toxicity the fibre might possess. For synthetic vitreous fibres, there is evidence from studies in animals that the potential for carcinogenicity increases with biopersistence (IARC, 2012; WHO, 2005). RAC recognised that glass microfibres which have the relevant dimensions and which are bio-persistent should be considered *de facto* carcinogenic.

RAC also recognizes that inhalation, is the major route of exposure in humans and therefore relevant for classification. Oral and dermal exposure routes are not considered relevant for glass microfibres. However, other non-physiological routes (e.g. intraperitoneal) and exposure regimens (e.g. single intratracheal administration) are considered relevant for hazard assessment. These non-physiological routes usually increase the sensitivity to a toxic response, mimicking worst-case exposure and biopersistence. According to WHO (2005), carcinogenicity testing of fibres by intraperitoneal injection represents a sensitive assay compared with rat inhalation studies.
The experimental data clearly provided evidence of a carcinogenic effect of E-glass microfibres by inhalation exposure in rats (Cullen *et al*. 2000). By intraperitoneal exposure, Cullen *et al*. (2000) showed an increase in the incidence of mesothelioma in rats. Besides, other studies from Pott (1984, 1987 and 1988) clearly report an increased incidence of abdominal tumours following intraperitoneal exposure to E-glass microfibres. This experimental data fulfils the criterion of sufficient evidence of carcinogenicity, since the carcinogenic effects were observed in two or more independent studies in one species carried out at different times or in different laboratories, or under different protocols.

Therefore RAC agrees with the proposal from the DS that E-glass microfibres warrant classification as Carc. 1B with hazard statement H350i: "May cause cancer by inhalation".

RAC also agrees with the proposed route-specific classification for inhalation (H350i). It is highly improbable that exposure by the dermal or even oral route would lead to a carcinogenic response, taking into account that long-term deposition of the E-glass microfibres in the tissues, as can occur in lung, is a prerequisite for carcinogenicity.

Comparison with criteria for applying notes specific to fibres

Note A, Q and R are specific to fibres and cover different aspects that condition their classification and labelling in Annex VI of CLP. The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 contain notes A, Q, R and A, R (respectively) which are described in Annex VI of the CLP Regulation.
The two existing entries in the CLP Regulation with index numbers 650-016-00-2 and 650-017-00-8 also contain notes A, Q, R and A, R (respectively) which are described as follows in Annex VI to the CLP Regulation:

Note A:

Without prejudice to Article 17(2), the name of the substance must appear on the label in the form of one of the designations given in Part 3 of Annex VI. In Part 3, use is sometimes made of a general description such as '... compounds' or '... salts'. In this case, the supplier is required to state on the label the correct name, due account being taken of section 1.1.1.4.

Note Q:

The classification as a carcinogen need not apply if it can be shown that the substance fulfils one of the following conditions:

— a short term biopersistence test by inhalation has shown that the fibres longer than 20 µm have a weighted half-life less than 10 days; or
— a short term biopersistence test by intratracheal instillation has shown that the fibres longer than 20 µm have a weighted half- life less than 40 days; or
— an appropriate intra-peritoneal test has shown no evidence of excess carcinogenicity; or
— absence of relevant pathogenicity or neoplastic changes in a suitable long term inhalation test.

Note R:
The classification as a carcinogen need not apply to fibres with a length weighted geometric mean diameter less two standard geometric errors greater than 6 µm.
The applicability or not of these notes is also part of the RAC opinion on E-glass microfibers and discussed further below.
For E-glass microfibres, RAC proposes to apply **note A** from Annex VI of the CLP Regulation, which states that without prejudice to Article 17(2), the name of the substance must appear on the label in the form of one of the designations given in Part 3. Table 3.1: List of harmonised classification and labelling of hazardous substances.

RAC is the opinion that E-glass microfibres should **not** be marked with **note R** from Annex VI of the CLP Regulation, which states that "*classification as a carcinogen need not apply to fibres with a length weighted aerodynamic geometric mean diameter less two standard geometric errors (LWGMD) greater than 6 µm*". The test method was published in Commission Regulation (EC) No 761/2009 (EC, 2009). The measurement method for the LWGMD under note R was created to characterise the fibre diameter of bulk substances or products containing man-made mineral fibres (MMMF, including Refractory Ceramic Fibres, man-made vitreous fibres (MMVF), crystalline and polycrystalline fibres. The length weighting is a means of compensating for the effect on the diameter distribution caused by the breakage of long fibres when sampling or handling the material. Geometric statistics (geometric mean) are used to describe the size distribution of MMMF diameters, because their diameters usually approximate to log normal distributions (ECB, draft 4). RAC concluded that note R is a measure for diameter and not length. The methods of manufacture given in the name of the entry (rotary and flame attenuation) and the name itself 'microfibres' also discount continuous filaments and also would not generate fibres with diameters > 6 µm. Indeed, the typical methods of manufacturing processes reported in publicly available literature (i.e. mostly from industry) are flame attenuation and rotary process, which determine the diameter of the fibre. The ranges of nominal diameters produced for these microfibres are less than 3 microns for rotary blowing process and less than 2-4 microns for flame attenuation process. This means that the LWGMD is not applicable to E-glass microfibres.

RAC is also of the opinion that E-glass microfibres of representative composition should not be marked with **note Q**. Indeed, the experimental evidence shows biopersistence and excessive carcinogenicity which does not allow an exemption of the classification as a carcinogen.

Finally, with regards to the identity of the substance, it is stated that "additional individual elements may be present at low levels". These elements, although at low levels and dependent on the manufacturing process, may influence both the toxicity and the biopersistence of the glass microfibres. It is also stated in the substance identity that "the process list does not preclude innovation" because there may be other "fiberisation" technologies or methods not covered in the proposed naming (e.g. Fi-high speed F-Technology).

Additional references

EC (2009) Commission Regulation (EC) No 761/2009 of 23 July 2009 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (Text with EEA relevance).

ECB (draft 4 under revision) ECB/TM/1(00) rev.2. Length weighted aerodynamic geometric mean diameter of fibres. Accessed on 09/02/2015 at

http://tsar.jrc.ec.europa.eu/documents/Testing-Methods/DRAFTIwgmd-4.pdf

IARC (2012). Arsenic, metals, fibres, and dusts. Monographs on the evaluation of carcinogenic risks to humans. Volume 100 C.

WHO (2005). Report of the World Health Organization workshop on mechanisms of fibre carcinogenesis and assessment of chrysotile asbestos substitutes. 8–12 November 2005, Lyon, France.

Campopiano A, Cannizzaro A, Angelosanto F, Astolfi ML, Ramires D, Olori A, Canepari S, Iavicoli S (2014). Dissolution of glass wool, rock wool and alkaline earth silicate wool: Morphological and chemical changes in fibers. Regul. Toxicol. Pharmacol. 70:1, pp. 393-406.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report and response to comments provided by the Dossier Submitter and by RAC (excl. confidential information).